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Article

Consequences of the COVID-19 Pandemic on the Incidence, Management and Outcomes of *Staphylococcus aureus* Bacteremia. Experience in a Spanish Hospital

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Abstract: This work aims to assess the impact of the COVID-19 pandemic on mortality and incidence of complications in patients with bacteremia due to *Staphylococcus aureus* (BSA). All episodes of BSA at the Costa del Sol University Hospital (Marbella, Spain) were recorded during the acute phase of the COVID-19 pandemic (March 2020 - March 2022), compared with a previous period (February 2018 - February 2020). Demographic, clinical and prognostic variables were recorded. The outcome was measured as 14 and 30-day mortality and the incidence of complications-death. Mortality during the pandemic was 28.7% at 14 days and 35% at 30 days, while in the pre-pandemic group it was 18.9% and 23.3%, respectively. In overall complication-death, the incidence rate is higher in the pandemic group with 42.7%. No significant differences were obtained between groups. 17 patients with COVID-19 were identified, with a mortality rate of 64.7% and 70.6% at 14 and 30 days. Multivariate analysis established the presence of sepsis at diagnosis as a predictor of mortality, but not BSA during the pandemic phase. In conclusion, BSA is a disease with high mortality, slightly higher during the pandemic phase. No differences were found in adherence to the bundle in our centre.

Keywords: *Staphylococcus aureus*; bacteremia; COVID-19; mortality; complications; adherence; bundle; nosocomial

1. Introduction

COVID-19, a primarily respiratory disease caused by the SARS-CoV-2 virus, has caused a social crisis and a challenge for science and healthcare systems, forcing us to change the way we understand medical practice in a context of uncertainty, stress, saturation of healthcare services, a new disease etc. Furthermore, it has affected the way in which multiple diseases are addressed, due to their contagiousness and the morbidity and mortality they have produced.

On the other hand, bacteremia by *Staphylococcus aureus* (BSA) is very common in our environment, with around 50 cases/100,000 people-year, and involves significant morbidity and mortality, with a mortality rate of around 20-30% [1–6]. This is the bacteremia with the highest mortality rate in global figures [7]. It has been the subject of study on multiple occasions with the aim of developing packages of measures or bundles to unify the way of approaching this entity and thus reduce mortality [8,9]. Despite this, however, there is still no uniformity in the way this entity is approached, with variability existing among professionals. The main factors that influence mortality are age and the presence of sepsis at diagnosis, as well as the early choice of an appropriate antibiotic, and not so much the virulence and resistance characteristics of the bacteria [5,10]. The way BSA occurs

varies, which makes it difficult to understand. The clinical incidence may correspond to various sources of infection that cause bacteremia or to the consequences of bacteremia (for example, remote embolisms).

This difficulty in identifying BSA increased during the COVID-19 pandemic period given that it is a disease that has been incorporated into the differential diagnosis as an infectious process, delaying its diagnosis and treatment. There are studies on BSA which maintain that the difference in mortality rates between centres could be due to different ways of caring for patients, so the management of bacteremia in each centre could have been different in the face of a health crisis situation, since this represents a relevant change in normal practice (6).

As with other respiratory viral infections, there is a predisposition to bacterial and fungal co-infection for several reasons: parenchymal destruction, cytokine storm and alteration of the immune system. Unlike infection by the influenza virus, also associated with bacterial co-infection, there is a low proportion of community acquisition of the disease. Due to their serious condition, COVID-19 patients are in closer contact with healthcare personnel, receive care (including being placed in a prone position), undergo interventions such as catheterisations, or receive immunosuppressive drugs. *S. aureus* is one of the most frequently isolated microorganisms in blood cultures in patients with COVID-19 [11–16] and is the most frequently isolated in respiratory samples in patients in intensive care [17,18]. Higher mortality has been described in patients who have suffered from COVID-19, especially when they are admitted to the intensive care unit or undergo mechanical ventilation [16,19–21].

Antimicrobial Stewardship Programs aim to improve the prognosis of infections. They were affected by the COVID-19 pandemic due to the organisational changes that this infection brought about in hospitals and in the way they care for their patients. On the one hand, there are studies that claim that the implementation of measures to reduce the transmission of infections (emphasis on hand hygiene, restrictions on visits, extensive disinfection of certain areas, use of masks, etc.) have reduced the transmission of infection, and with them the incidence of bacteremia by *S. aureus* or infection by *Clostridioides difficile* [22]. On the other hand, other studies show that the incidence rate is higher [16]. The information coming from studies regarding the impact of the pandemic on the incidence, management and outcome of this bacteremia is heterogeneous, which is why the present study has been proposed to help increase knowledge regarding mortality and complications with the aim of improving care for these patients.

The aim of this study was to assess the impact of the acute phase of the COVID-19 pandemic on mortality and incidence of complications in adult patients with BSA, comparing it with a period prior to that phase.

2. Materials and Methods

Observational and retrospective study including non-paediatric patients (≥ 14 years) with bacteremia documented by blood culture for *S. aureus* included in the bacteremia registry of our centre (Costa del Sol University Hospital, Marbella, Malaga, Spain) during the acute phase period of the COVID-19 pandemic in Andalusia (according to the COVID-19 report in Andalusia, from 1 March 2020 to 31 March 2022) [23]. They were compared with a period of equal duration, established between 1 February 2018 and 29 February 2020. Demographic, clinical and prognostic variables were collected from the digital medical record. Cases with persistent bacteremia were considered as a single patient. Patients who did not complete treatment at our centre or in the public hospital network of Andalusia were excluded.

Healthcare-related acquisition was defined as that in which patients were in a nursing home, attended a dialysis centre or outpatient clinic, and nosocomial acquisition as that in which bacteremia occurred more than 48 hours after admission. The source of infection was defined by clinical data collected in the medical history, by microbiological criteria (isolation of *S. aureus* in other clinical samples) or both. Antibiotic treatment was classified as empirical or directed based on whether the prescription was made before or after the results of the blood cultures were known, respectively; and the adequacy of the treatment in terms of spectrum coverage and dosage according to the latest

guidelines for the treatment of bacteremia [24,25]. Compliance with the bundle was defined as an adequate duration of treatment, performance of control blood cultures 48-72 hours after starting appropriate treatment and performance of an echocardiogram in the case of clinical indication (individual risk, persistent bacteremia, complicated bacteremia, community acquisition or unknown cause [4]). Those who had received adequate duration of treatment based on the underlying clinical process and individual risk, who had undergone echocardiography and control blood cultures, were identified. Persistent bacteremia was defined as that with isolation of *S. aureus* in control blood cultures 48-72 hours after starting appropriate treatment. The appropriate treatment duration was considered to be 14 days for uncomplicated bacteremia, and longer depending on whether the bacteremia was complicated or whether the cause or complications arising from the bacteremia required a longer duration.

Microbiological identification was performed directly from the positive blood culture using mass spectrophotometry. (MALDI-TOF, Bruker Daltonics, Billerica, Massachusetts). Following the identification of *S. aureus*, a polymerase chain reaction (PCR) was performed directly from the positive blood culture for the early detection of methicillin resistance (*mecA/mecC*) (BD MAX StaphSR Assay (SR assay; BD, USA). The antimicrobial susceptibility report was performed using the turbidimetric method (Vitek 2, Biomérieux, Marcy-l'Étoile, France). The detection of *S. aureus* in other clinical samples (catheters, respiratory samples, etc.) was also performed using MALDI-TOF from the culture. SARS-Cov-2 detection was performed using multiple commercial PCR kits in nasopharyngeal swab samples.

The main variables to determine the impact of the COVID-19 pandemic on mortality due to BSA were mortality at 14 and 30 days from the first positive blood culture, the presence of sepsis at diagnosis, the development of complications (defined as endocarditis, osteoarticular, myositis, aortitis, lung abscess, central nervous system abscess, abscess in another location or others), the presence of persistent bacteremia and adherence to the measures recommended in the bundle from BSA.

A descriptive analysis was performed using measures of central tendency, dispersion and position for quantitative variables, and frequency distribution for qualitative variables. For each of the dichotomous outcome variables of interest, bivariate analysis was performed using the Chi-square test (or Fisher's exact test) for qualitative independent variables, and the Student t test (or Mann-Whitney U test in the case of non-normal distribution) for quantitative independent variables. A multivariate logistic regression model was then constructed for the outcome variables (mortality at 14 and 30 days, together with the combined variable presence of mortality or complication at 30 days), using the forward stepwise method with independent variables of interest (group, age, sex and Charlson index), and describing odds ratios (OR) with respective 95% confidence intervals. In the different analyses, the level of statistical significance was established at $p < 0.05$. SPSS v28 software was used.

This study was approved by the Costa del Sol Research Ethics Committee with the code: 004_dic23 – PI on December 21, 2023.

3. Results

A total of 31,820 hospital admissions for any cause were recorded in adults during the acute phase of the pandemic, hereinafter referred to as the pandemic period, and 34,371 admissions in the pre-pandemic period. A total of 212 episodes of bacteremia were obtained in the study period, 122 corresponding to the pandemic phase group and 90 episodes to the comparison group. The risk of developing BSA during the pandemic period was 3.83 per 1000 hospital admissions and in the pre-pandemic period it was 2.62 per 1000 admissions ($p = 0.09$).

Demographic and clinical variables are described in Table 1. Males predominated, with 69.7% and 74.4% in the pandemic and pre-pandemic groups respectively. The mean age ($\pm$ standard deviation) in the pandemic and pre-pandemic periods was 66 (± 15) and 63 (± 17), respectively. There were no significant differences in comorbidities between both groups. More than half of the infections in the pandemic group were of nosocomial origin (54.1%), which is statistically significant. Regarding

the cause of infection, the two most frequent groups in the pandemic group were skin and soft tissue infection (SSTI) and respiratory origin, without reaching statistical significance in the latter case. In the pre-pandemic group, the most frequent causes were catheter-associated infection and SSTI. Primary bacteremia cases were 12.3% in the pandemic phase and 16.7% in the pre-pandemic phase, with no differences between groups.

Table 1. Demographic and clinical characteristics.

		Pre-pandemic period	Pandemic period	p
Sex (male); N (%)		67 (74.4)	85 (69.7)	0.54
Age; Mean years (SD)		63 (17.1)	66.3 (15.5)	0.21
Charlson index; Median (P25 - P75)		2 (1 - 4.3)	2 (1 - 3.3)	0.03
Pitt Score; Median (P25 - P75)		1 (0 - 2)	0 (0 - 3)	0, 08
McCabe; N (%)	Not fatal	33 (36.7)	49 (40.2)	0.13
	Quickly fatal	25 (27.8)	46 (37.7)	
	Finally fatal	32 (35.6)	27 (22.1)	
Bacteria; N (%)	MSSA	85 (94.4)	114 (92.6)	0.80
	MRSA	5 (5.6)	9 (7.4)	
Acquisition; N (%)	Community	29 (32.2)	31 (25.4)	-
	Related to healthcare	26 (28.9)	25 (20.5)	
	Nosocomial	35 (38.9)	66 (54.1)	
Source of infection; N (%)	Catheter	30 (33.3)	25 (20.5)	0.05
	SSTI	20 (22.2)	31 (25.4)	-
	Respiratory	12 (13.3)	26 (21.3)	0.19
	Endocarditis	4 (4.4)	8 (6.6)	-
	Osteoarticular	4 (4.4)	4 (3.3)	
	Abdominal	1 (1.1)	7 (5.7)	
	Urinary	3 (3.3)	5 (4.1)	
	Others	1 (1.1)	1 (0.8)	
	Primary	15 (16.7)	15 (12.3)	0.48
N: total number of patients in that category. SD: standard deviation. P25: 25th percentile. P75: 75th percentile. MSSA: Methicillin-sensitive <i>S. aureus</i> . MRSA: Methicillin-resistant <i>S. aureus</i> . SSTI: skin and soft tissue infection				

Regarding the outcome of bacteremia, in the pandemic phase group there was a mortality rate of 28.7% at 14 days and 35% at 30 days, while in the pre-pandemic group it was 18.9% and 23.3%, respectively. In the overall complication-death, the incidence rate is higher in the pandemic group with 42.7% of patients. However, no significant differences were obtained between both groups (Table 2).

Table 2. Outcome.

		Pre-pandemic period	Pandemic period	p
14-day mortality; N (%)		17/90 (18.9)	35/122 (28.7)	0.14
30-day mortality; N (%)		21/88 (23.3)	42/120 (35)	0.09
Complication/death at 30 days; N (%)		29/88 (33)	50/120 (41.7)	0.25
Complications; N (%)	None	63/78 (80.8)	83/97 (85.6)	-
	Endocarditis	7/78 (9)	5/97 (5.2)	
	Osteoarticular	2/78 (2.6)	3/97 (3.1)	
	Abscess/myositis	4/78 (5.1)	3/97 (3.1)	

	Pulmonary embolisms	4/78 (5.1)	3/97 (3.1)	
	Embolisms CNS	1/78 (1.3)	4/97 (4.1)	
	Others	1/78 (1.3)	0/97	
	Persistent bacteremia; N (%)	8/80 (10)	13/100 (13)	0.26
	Sepsis at diagnosis; N (%)	29 (32.6)	44 (38)	0.51
	Early empirical therapy (before 24h); N (%)	70 (80.5)	113 (94.3)	0.005
	Adequate empirical therapy; N (%)	68 (79.1)	103 (88)	0.12
	Adequate empirical dose; N (%)	61 (71.8)	96 (89.7)	0.03
	Adequate targeted therapy; N (%)	75 (94.9)	100 (95.2)	1
	Adequate targeted dose; N (%)	72 (90)	96 (91.4)	0.94
N: total number of patients in that category. CNS: central nervous system				

Of the variables analysed in the multivariate model, a relationship was found between developing the complication-death complex with sepsis at diagnosis ($p < 0.001$) with an OR of 4.96. The risk of incidence of the complication-death complex in relation to age is p 0.06. There were no differences between groups regarding the presence of complications-death.

Regarding adherence to the measures recommended by the antimicrobial stewardship consultancy and the degree of compliance with the bundle, no significant differences were found between groups (Table 3).

Table 3. Adherence to the *bundle*.

	Pre-pandemic period	Pandemic period	p
Adequate duration; N (%)	44/67 (65.7)	53/80 (66.3)	1
Echocardiogram; N (%)	65/81 (80.2)	80/103 (77.7)	0.8
Control blood cultures; N (%)	50/80 (62.5)	59/100 (59)	0.82
Compliance with all recommendations; N (%)	38 (50.7)	54 (54.5)	0.72
N: total number of patients in that category			

3.1. Bacteremia in Patients with COVID-19

17 patients with COVID-19 were identified in the pandemic group (13.95% of the total) (Table 4). Infection acquisition is mostly nosocomial, with 82.4%. The most frequent focus was respiratory (52.9% of cases). Regarding 30-day mortality, 5 deaths can be attributed to COVID-19 and 5 to BSA, with data missing for 2 patients.

Table 4. Bacteremia in a patient with COVID-19.

			p
	Bacteria MSSA; N (%)	16 (94.1)	1
	Community	0	-
Acquisition; N (%)	Related to healthcare	3 (17.6)	-
	Nosocomial	14 (82.4)	0.007
	Source of respiratory infection; N (%)	9 (52.9)	0.001
	Source of catheter infection; N (%)	4 (23.5)	-
	14-day mortality; N (%)	11 (64.7)	<0.001
	30-day mortality; N (%)	12 (70.6)	<0.001
	Complication/death at 30 days; N (%)	12 (70.6)	0.005
N: total number of patients in that category. MSSA: Methicillin-sensitive <i>S. aureus</i>. N: total number of patients in that category.			

4. Discussion

This study investigated the outcome of BSA in the Costa del Sol University Hospital in Marbella (Malaga, Spain) during the COVID-19 pandemic period, with the aim of clarifying whether this health crisis has led to an increase in the mortality or incidence of complications of this bacteremia, as well as to elucidate whether there have been changes in its incidence and management during the study period. It represents the work with the largest sample size compared to other studies with similar objectives [10].

The incidence of BSA was slightly higher during the pandemic period, although no significant differences were found when compared to the pre-pandemic period. This incidence is variable in the literature; on the one hand, there are studies that found a higher incidence of both community-acquired and nosocomial BSA during the pandemic (attributed to the delay in treatment, the severity of COVID-19 patients, the widespread use of antibiotic therapy or greater exposure to invasive procedures or lower use of infection control measures [16,19,26]); on the other hand, other studies found a significantly lower incidence of nosocomial BSA during the pandemic, attributing it to the reduced contact of the patient with the staff, the restriction of visits and the use of masks and the decontamination of surfaces [22].

In both groups, there is a predominance of male patients, slightly higher in the group of the acute phase of the pandemic, but with the same comorbidity burden according to the Charlson index and the same severity according to the Pitt score. The patients included in the sample have similar characteristics with regard to other multi-centre studies, such as age around 65 years and median comorbidity calculated by the Charlson index of 2 [6]. We found a low prevalence of methicillin-resistant *S. aureus* (MRSA) in our centre, 7%, somewhat lower than in other Spanish centres [11], similar to other European studies [10]. There was a slight increase in cases of MRSA bacteremia during the pandemic period, although without statistically significant differences, probably due to the sample size. Other authors have found an increase in MRSA bacteremia during the pandemic, which is attributed to the practically universal use of antibiotic therapy in their patients with COVID-19 pneumonia [5].

The distribution of the causes of BSA between both groups is similar to that described by other authors, with a non-significant increase in the respiratory focus in the pandemic group consistent with other series [11], even above other more frequent foci of infection in the literature such as catheter-associated infection [10]. There is a lower representation in both groups of primary BSA compared to other series - around 20-40% (2.6) - which could be related to the insistence on the investigation of cases in both study periods by the antimicrobial stewardship consultancy after learning the positive result of the blood culture.

Regarding the form of acquisition of BSA, in our centre nosocomial acquisition was 54.1% in the pandemic phase, with significant differences when compared to the pre-pandemic phase (38.9% of cases). There is heterogeneity in the studies regarding hospital or nosocomial acquisition, between 45-70% [6,10].

In the periods studied, there was an increase in the pandemic period in mortality at 14 and 30 days, as well as in the global death-complications, but not significantly. In addition, 30-day mortality was slightly higher (35%) than most of the studies, which establish it between 20-30% in non-specific periods of the COVID-19 pandemic [1-6]. This mortality rate was surpassed during the pandemic period by a hospital in Tehran (Iran) with 41.9% of mortality [5] and only in this centre do they describe a lower incidence of mortality in non-COVID-19 patients than previously reported, which they relate to a small sample size and comparison with an older national cohort [13]. In another work reported by Böing et al., changes in the prognosis were observed, and although it has a smaller sample size, they relate it with good adherence to the bundle [10]. The incidence of complications arising from bacteremia has not been studied in any work. In the literature, the main causes of mortality associated with BSA are respiratory focus and primary bacteremia [3,6]. In our study, the slight increase in mortality was accompanied by an increase in respiratory causes and a decrease in primary BSA, but both without significant differences. The logistic regression model performed also did not find significant differences for the variables studied, probably due to the sample size.

In our centre, each bacteremia reported from the Microbiology laboratory is communicated to the antimicrobial stewardship expert. It is the task of the expert to locate the doctor responsible for the patient, inform him/her and make recommendations on how to proceed, mainly verbally and occasionally in writing, or to locate the patient at home if he/she has been discharged from the emergency department. This means that all cases of bacteremia have been advised by the antimicrobial stewardship expert except those with an early fatal outcome. This continued during the acute phase of the pandemic despite the overload of care facilities. Several studies highlight the role of the infectious disease consultant in improving the prognosis of this disease [2–4]. In some centres there was less consultation and less adherence to recommendations during the pandemic period [9]. However, in our study, adherence was observed for around 50% in both periods for compliance with all the measures recommended in the bundle. Adherence was slightly higher in the pandemic group, but not significantly, increasing from 50.7% to 54.5%, similar to other studies with a retrospective nature [27]. This greater adherence may be due to greater awareness regarding disease management after each contact with the antimicrobial stewardship team; however, we think that the lack of generalisation of written recommendations in a place with a high turnover of responsible physicians (on-call, consultations, etc.) could have had a significant impact on overall adherence to the measures of the bundle in our centre. In other studies [8] adherence to the bundle was higher, probably because they are within prospective or quasi-experimental studies and do not deal with real-life data, although there are also prospective studies with low adherence, around 18%, which relate this low adherence despite being a prospective study due to the heterogeneity of the participating centres, with worldwide distribution [28].

5.1. Bacteremia in Patients with COVID-19

In our patients, 17 suffered from COVID-19, with a mortality at 14 and 30 days of 64.7 and 70.6%, respectively, practically double the mortality of patients who did not suffer from it, much higher and significantly higher than in other studies with a similar population, where they also do not observe differences with patients without COVID-19 [11]. However, this is probably an over-represented mortality due to the small sample size. The increased mortality compared to other patients with BSA is supported by other studies where it has been found that co-infected patients have higher mortality, as well as a higher incidence rate of shock and respiratory failure. These mortality data are explained by nosocomial acquisition, the use of immunosuppressive drugs, the interventionism to which they are subjected with greater difficulty in practising nursing procedures due to contact precautions or the characteristics of the virus [12–15].

The main form of acquisition is nosocomial, as in other works, and the source of infection is usually also respiratory [11,29], except in the work of Mason [16] where catheter-associated bacteremia is greater than the respiratory origin of the infection, which is related to the change in the staff/patient ratio and the interventionism to which they are subjected.

5. Limitations

The main limitations of this study were its single-centre nature and retrospective design. It should be noted that the nature of the design did not contemplate the calculation of a sample size for the detection of differences in both groups, so the differences may be underestimated. Furthermore, mortality attributable to bacteremia or other causes, including COVID-19, has been interpreted based on information collected in the medical history and has often been of unknown origin.

6. Conclusions

The severity and complexity of BSA requires a group of experts in each hospital, dedicated to advising and monitoring this process, preferably at the bedside. Health emergency situations put these measures in jeopardy, where efforts were redirected in the case of the COVID-19 pandemic to the care of these patients. Although a trend has been observed, no statistically significant differences have been found in terms of mortality or complications in patients treated for BSA during the COVID-

19 pandemic. New studies with a larger sample size are necessary to analyse these data, as well as the risk factors that could explain this worse prognosis.

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